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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/977,787	11/25/1997	LEE MIZZEN	STS96-02A	3496
26161	7590	06/16/2005	EXAMINER	
FISH & RICHARDSON PC 225 FRANKLIN ST BOSTON, MA 02110			ZEMAN, MARY K	
			ART UNIT	PAPER NUMBER
			1631	
DATE MAILED: 06/16/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

08/977,787

Applicant(s)

MIZZEN ET AL.

Examiner

Mary K. Zeman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 3/28/05.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 54,57-59,61-69 and 88-98 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 54,57-59,61-69 and 88-98 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

Applicant's arguments with respect to claims 54, 57, 58, 59, 61-69, 88-98 have been considered but are moot in view of the new ground(s) of rejection.

Claims 54, 57, 58, 59, 61-69, 88-98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 (CAFC 1988). The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below which leads to the determination that the above claims lack enablement due to undue experimentation being required to make and use the invention.

For enablement purposes, the experimentation which is necessary must be directed to the requirements under 35 USC 112, first paragraph, as summarized in the MPEP in 2162 which states that "the patentee must disclose in the patent sufficient information to put the public in possession of the invention and to enable those skilled in the art to make and use the invention." Thus, both making the invention must be enabled as well as a use thereof. The MPEP further summarizes these requirements in section 2164.01 in the "Test of Enablement" via stating that "Accordingly, even though the statute does not use the term 'undue experimentation,' it has been interpreted that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation." The MPEP further states in section 2164.01 that "The fact that experimentation may be complex does not necessarily make it undue,

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if the art typically engages in such experimentation.” Further, “The test of enablement is not whether any experimentation is necessary, but whether if experimentation is necessary it is undue.” The MPEP then summarizes the below factors for the determination of the enablement requirement in 2164.01(a) as also set forth above as the so called Forman Factors. In the MPEP at section 2164.01(b), third paragraph, a key issue that can arise in the biotechnical area is the availability of starting materials to make the invention, especially when such availability is present “only after extensive screening.” The MPEP at section 2164.01(c) further summarizes that requirement of a use for the claimed invention is included either as recited or based on knowledge of similar inventions, described as exemplified in relationship to compounds. Lastly, it is acknowledged that the specification does not need to disclose what is well known to those skilled in the art as described in the MPEP at section 2164.05(a), 6<sup>th</sup> paragraph.

The MPEP at 2164.04 requires that it is necessary to firstly construe the claims before any analysis of enablement can occur. Thusly the above rejected claims 54, 57, 58, 59, 61-69, 88-98 are construed to be directed to a polypeptide of an antigen of an influenza virus (or an unidentified antigenic prortion thereof) and a stress protein (or an unidentified portion thereof), or the following variants: a polypeptide comprising at least an immunogenic portion, such that the ability of the variant to induce a specific immune response is not substantially diminished. This polypeptide is construed as being prepared via host cell culturing wherein the host cell contains a vector which in turn contains a polynucleotide made up of normally found nucleotides which encode the polypeptide recited above via the translation of normally occurring triplet codons therein into said polypeptide.

Given the above summaries, it is appropriate to turn to consideration of the factors determinative of enablement regarding whether undue experimentation is required to enable the claimed invention.

The eight factors are summarized below regarding supporting the above rejection.

(1) – the quantity of experimentation necessary-

There are an enormous number of polynucleotides, vectors, and host cells to be experimentally tested in order to make a useful polypeptide of a fusion protein comprising one of 7 influenza proteins (or portions thereof) in fusion with unnamed stress proteins (or portions thereof. Regarding the polynucleotides to be tested, the art recognizes that for each amino acid

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in the claimed fusion proteins that there are degenerate codons available as shown in the well known Biochemistry textbook by Lehninger as in Table 31-5 on page 718. Counting the number of codons results in observing that 5 of the normal amino acids may each be encoded by one of 4 three nucleotide codon options. For 9 of the normal amino acids, 2 such three nucleotide codon options are available. For 3 amino acids, 6 such codon options are available. For 1 amino acid, 3 such codons are utilized. For 2 amino acids, only one such codon is available. An average of the number of codons per amino acid may be approximated via an averaging of the above codon usage as being three available codons for an average amino acid. Without specifying the length of a sequence encoding the claimed fusion proteins, it may be reasonably approximated that it is a polypeptide which falls within the range of polypeptides with sizes as shown in the well known Biochemistry textbook by Lehninger as in Table 3-2 on page 57. A median polypeptide contains 550-800 amino acids. Choosing conservatively, a median polypeptide thus contains 500+ amino acids. Therefore, an estimate of the number of potential polynucleotides encoding the claimed proteins of 500 amino acids would be that calculated at 3 raised to the 500<sup>th</sup> power. This further calculates to approximately  $10^{240}$  possible polynucleotides to evaluate or experimentally test to find those useable in making a useful fusion polypeptide, or a polypeptide meeting the limits of the genus of polypeptides in claims 54. Thus, there is an enormous number of polynucleotides to experimentally test to find any that encode the claimed fusions or its variants which are useful. Another experimentation requirement regarded to enable the use of the instantly claimed methods is the determination of a useful activity for the claimed fusion polypeptides. The file history indicates that a specific fusion polypeptides comprising specific stress proteins with specific influenza antigens is useful in provoking an immune response against the influenza antigen. Antigenicity, or the ability to provoke a specific immune response is strongly dependent on the three dimensional structure of the polypeptide. In the well known Biochemistry textbook by Lehninger at pages 58-62, not only is the vast diversity of protein polypeptides set forth regarding functionality, such as enzymatic function, but that each protein has a characteristic three-dimensional shape referred to as its conformation. The specification and claims have not disclosed what portions of the parts of the fusion protein are required for antigenicity, and to test for this factor alone relegates the experimentation to undue experimentation regarding a lack of any indication of what experimental test or assay is to be performed. This experimental search

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for a test is further complicated by a lack of any guidance regarding what single, or even a subset of polynucleotides out of the  $10^{240}$  should be tested. These considerations are supportive of a determination of undue experimentation to find a starting material polynucleotide to be placed in a vector and in turn a host cell for culturing, for production of a polypeptide to be used as claimed.

Turning to the question of what host cell is to be utilized in producing the polypeptide, it is well known that a myriad of thousands of cell types are known to Biotechnology. It is acknowledged that some of these known cell types are more commonly utilized for host cell culturing as described in the specification. Even such commonly utilized host cells number into the hundreds. In USP 5,082,767, Hatfield et al., the expression of polynucleotides in host cells of various types is described in column 1 lines 1-49. Even though such expression practices are frequently carried out, Hatfield et al describe another major problem in this area in column 1 lines 50-65, wherein a protein (or polypeptide) is produced in recoverable quantities, but is inactive. As discussed above, some type of activity (antigenicity) is required for the polypeptide of the claims. A solution is described in Hatfield et al in column 1 lines 61-65 as elusive and is apparently related to an unpredictability in proper protein folding during expression. In column 1 line 66 through column 2 line 59, various codon usage and context effects are described as problematic. In column 2 lines 53-59 the predictive value of statistical rules for preferred nucleotides adjacent to codons is described as relatively low. Hatfield et al go on to analyze codon pair usage frequencies wherein optimization of codon pair usage is then derived for determining polynucleotides which encode a protein or polypeptide in order to achieve an active polypeptide when made via a host cell culture such as described herein. This process, however, is complex and requires very specific host cell and polypeptide correspondence in order to perform the analysis to then make a useful and active protein. It is noted that the instant disclosure lacks any codon pair frequency analysis description for even a single host cell type. The Hatfield et al disclosure is a single procedural description which still lacks indication of how someone of skill in the art would test for appropriate antigenicity on which to base the codon usage analysis as disclosed therein. Thus, there would be no predictability as to what to direct a codon pair usage determination to as set forth in Hatfield et al. for the making of an active polypeptide. It is also pointed out that Hatfield et al. is a single disclosure and as such is not a

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well known practice for enabling the instant invention, and thus not available to applicant on this basis. Another disclosure of unpredictability in the art of codon usage is that of Nagata et al. (BBRC 261: 445-451 (1999)) wherein obstacles are summarized for the expression of genes in host mammalian cells on page 445, first paragraph after the abstract. Nagata et al. further describes an indication that codon study to clarify codon usage as related to polypeptide expression is known on page 445, second column lines 31-34. Nagata et al. was published years after issuance of the above cited Hatfield et al patent, and additionally documents the Hatfield disclosure as not being well known. Applicants cannot rely on a procedure in Hatfield et al as well known to assist in enabling the claimed invention.

Applicant may argue that inoperative subject matter is permitted in a claim and that generic polynucleotides that contain codons corresponding to encoding the generic fusion proteins which are inoperative are thus permitted within the scope of the claim. Consideration, however, of the MPEP at section 2164.08(b) regarding inoperative embodiments reveals that the standard is whether a skilled person could determine which embodiments, that were conceived, but not yet made, would be inoperative or operative with no more effort than is usually required in the art. This argument, however, would not be persuasive as some type of operativeness test would reasonably be required in order to make this determination. As discussed above, the myriad of possible testing for active polypeptides reasonably would require undue experimentation itself. Normally in the art, a specific test would be required for polypeptide activity assessment even if cultured as described. Such a test is not apparent for assessment of operative vs inoperative polynucleotides and host cells for preparation of a useful fusion polypeptide.

This, in summary, the above described unpredictability for polynucleotide testing, or even what test to perform as well as host cell selection with corresponding codon, codon pair and/or codon context practice is supported by the number into enormous possibilities. No instant guidance to reasonable narrow the required experimentation leads to a determination of undue experimentation being required for both polynucleotide selection, and host cell selection that would result in an active and therefor useful fusion protein of an influenza protein and an unnamed stress protein or variant thereof.

(2) – the amount or direction presented-

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None other than the above described general knowledge in the art, which still leaves undue experimentation for enabling the instant invention.

(3)- the presence or absence of working examples-

Specific fusion proteins, such as pET65MP/NP-B, pET65MP/NP-D are disclosed. Claims limited to these would be enabled. Specific influenza antigens named in the specification (and the claims) include nucleoprotein, neuraminidase, M1, M2, PB1, PB2 or PA, however, specific antigenic portions of those proteins are not specifically disclosed. No specific sequences of these proteins are disclosed. Specific stress proteins disclosed in the specification (and claims 92-94) include hsp65, hsp71, Hsp100-200, hsp90, LON, Hsp70, hsp60, TF55, Hsp40, FKBP, cyclophilin, Hsp20-30, C1pP, GrpE, Hsp10, ubiquitin, calnexin, or protein disulfide isomerase. Specific portions of these proteins which are useful in the fusion proteins are not disclosed in the specification. The specification does not provide any specific sequences for any of the stress proteins such that one of skill in the art would be able to make any of the stress proteins or fragments thereof. Claims limited to specific influenza antigens and specific stress proteins may overcome this rejection.

(4)- the nature of the invention-

The invention is complex as there is no guidance as to which polypeptides, out of myriads possible to test for ability to generate a specific immune response once prepared. Even testing of polypeptide activity is generally a detailed process.

(5)- the state of the prior art-

Although many polypeptides have been cloned and expressed in culture, the Hatfield et al. summary indicates that the cultural expression of an active polypeptide is elusive and subject to many complex factors.

(6)- the relative skill of those in the art-

The cultural expression of polynucleotides in vectors in host cells to make a polypeptide is generally performed by graduate level or even more highly skilled individuals and is subject to numerous complex considerations for successful results. Even with this skill level, an unsuccessful result is frequently obtained, as noted above by Hatfield et al.

(7)- the predictability or unpredictability of the art-



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The factors for making a useful and thus enabled polypeptide are elusive and unpredictable for a polypeptide wherein the polynucleotides which encode it for any host must be determined as described above.

(8)- the breadth of the claims-

The claims are directed to encompass a broad genus of unspecified fusion proteins. This is extremely broad regarding polynucleotides, vectors, and host cells that may be implemented in order to carry out the invention. As discussed above, the claim lacks any specificity as to what polynucleotides, vectors or host cells within this wide breadth of claim practice would be useable to result in the generation of an active polypeptide that can provoke the required response.

Thus, in conclusion, the above rejected claims lack enablement due to undue experimentation required to practice the claimed methods.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (571) 272 0723

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, PhD can be reached on (571) 272 0718. The fax phone number for the organization where this application or proceeding is assigned is 571 273 8300.


Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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MARY K. ZEMAN  
PRIMARY EXAMINER  
